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ATHEROSCLEROTIC DISEASE OF THE AORTIC ARCH AS A RISK FACTOR FOR RECURRENT ISCHEMIC STROKE

THE FRENCH STUDY OF AORTIC PLAQUES IN STROKE GROUP*

Abstract Background. Atherosclerotic disease of the aortic arch is found in 60 percent of patients 60 years of age or older who have had brain infarction. The aim of this study was to determine whether atherosclerotic plaques in the aortic arch are a risk factor for recurrent brain infarction and for vascular events in general (i.e., brain infarction, myocardial infarction, peripheral embolism, and death from vascular causes).

Methods. For a period of two to four years, we followed a cohort of 331 patients 60 years of age or older who were consecutively admitted to the hospital with brain infarction (a total of 788 person-years of follow-up). All patients underwent transesophageal echocardiography to determine whether atherosclerotic plaques were present in the aortic arch proximal to the ostium of the left subclavian artery. The patients were divided into three groups according to the thickness of the wall of the aortic arch (<1 mm, 1 to 3.9 mm, and ≥ 4 mm).

Results. The incidence of recurrent brain infarction was 11.9 per 100 person-years in patients with an aor-

tic-wall thickness of ≥ 4 mm, as compared with 3.5 per 100 person-years in patients with a wall thickness of 1 to 3.9 mm and 2.8 per 100 person-years in patients with a wall thickness of <1 mm ($P < 0.001$). The overall incidence of vascular events was 26.0, 9.1, and 5.9 per 100 person-years of follow-up in the respective groups ($P < 0.001$). After adjustment for the presence of carotid stenosis, atrial fibrillation, peripheral arterial disease, and other risk factors, aortic plaques ≥ 4 mm thick (including the thickness of the aortic wall) were found to be independent predictors of recurrent brain infarction (relative risk, 3.8; 95 percent confidence interval, 1.8 to 7.8; $P = 0.0012$) and of all vascular events (relative risk, 3.5; 95 percent confidence interval, 2.1 to 5.9; $P < 0.001$).

Conclusions. Atherosclerotic plaques ≥ 4 mm thick in the aortic arch are significant predictors of recurrent brain infarction and other vascular events. (N Engl J Med 1996; 334:1216-21.)

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IN the past few years, evidence has accumulated that atherosclerotic disease of the aortic arch may be a source of cerebral emboli.¹⁻¹⁰ We previously found that the prevalence of ulcerated plaques in the aortic arch at autopsy increased with age and was independently associated with brain infarction of unknown cause.¹¹ We and others then found a strong association between protruding plaques in the aortic arch detected by transesophageal echocardiography and the risk of ischemic stroke.^{3,10,12,13} Plaques located proximal to the ostium of the left subclavian artery have been found in 60 percent of patients 60 years of age or older with ischemic stroke, but the association with ischemic stroke was particularly strong when the plaques were ≥ 4 mm in thickness.¹² Tunick et al.¹⁴ found an annual rate of vascular events of 33 percent in patients who had protruding plaques ≥ 5 mm thick in the thoracic aorta, as compared with 7 percent in matched control subjects. However, they considered plaques in the entire thoracic aorta, not just in the aortic arch, and the incidence of brain and retinal emboli was not significantly different between the two groups (seven events in the patients vs. three in the controls).¹⁴

We followed a series of patients consecutively admitted to the hospital with brain infarction. All of them underwent transesophageal echocardiography within 15

days after the qualifying brain infarction to detect plaques in the aortic arch. The aim was to determine the risk of recurrent brain infarction and of vascular events in general (recurrent brain infarction, myocardial infarction, peripheral embolism, and death from vascular causes) in patients with plaques in the aortic arch that were ≥ 4 mm thick (including the thickness of the aortic wall) as compared with patients with smaller plaques or no plaques.

METHODS

Patients

Patients 60 years of age or older with brain infarction who were hospitalized consecutively between September 1991 and October 1993 were enrolled in the study. Information was recorded about arterial hypertension, hypercholesterolemia, cigarette smoking, diabetes mellitus, body-mass index, previous myocardial infarction, previous brain infarction, previous transient ischemic attacks, peripheral vascular disease, and previously detected atrial fibrillation or atrial fibrillation recorded within eight days after the detection of the qualifying brain infarction. Within 15 days after the onset of the stroke, the patients underwent cranial computed tomography, magnetic resonance imaging of the brain, or both; ultrasound examination of the internal carotid and vertebral arteries (according to a standard protocol); transcranial Doppler examination; 12-lead electrocardiography; and transesophageal echocardiography, including an assessment of the thoracic aorta. Patients considered to have brain infarction of unknown cause had no detectable cause of stroke or had conditions that have not been shown to increase the risk of brain infarction in persons older than 60 years, such as ipsilateral carotid stenosis of 30 percent or less, patent foramen ovale, atrial septal aneurysm, or mitral-valve prolapse.

Three hundred thirty-five patients were enrolled in the study, but four were immediately lost to follow-up. Three hundred thirty-one patients were therefore followed, 102 of whom had brain infarction of unknown cause. The patients received standard medical therapy from their physicians for the secondary prevention of stroke and other vascular events. For antithrombotic therapy, patients with a qualifying brain infarction of known cause received the recommended treatment for secondary prevention (e.g., antiplatelet therapy if they had a stroke

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As the principal investigator, Dr. Amarenco assumes full responsibility for the overall content of the article.

*The institutions and investigators in the French Study of Aortic Plaques in Stroke Group are listed in the Appendix.

related to atherosclerosis and oral anticoagulant therapy if they had atrial fibrillation or another definite cardiac or arterial source of embolism). Patients were either examined at least once a year in an outpatient clinic (46 percent of patients) or interviewed by telephone (54 percent). In the latter case, family members or the personal physicians were also interviewed. We recorded new vascular events on follow-up. Brain infarction was recorded if there were new focal symptoms lasting more than 48 hours. Computed tomography was performed in 78 percent of patients with new symptoms, and a neurologic examination showed new focal deficits in 94 percent of them. We also recorded symptomatic retinal-artery occlusion, myocardial infarction (medical records were obtained in 75 percent of these cases), peripheral embolism (including documented lower-limb embolism or acute leg ischemia treated by amputation, acute renal failure, bowel infarction, and blue-toe syndrome), and death from vascular causes (including sudden death). Cerebral transient ischemic attacks and angina pectoris were not classified as new vascular events. We also recorded other nonvascular events and all deaths.

Transesophageal Echocardiography of the Aorta

Transesophageal echocardiography was performed as previously described¹² by experienced cardiologists who had no information about the underlying causes of the brain infarction. Videotapes of the transesophageal examinations of the 331 patients were reviewed by a senior echocardiographer according to a protocol that we have described previously.¹² The tapes were reviewed in random order, and the echocardiographer was unaware of the causes of the brain infarctions. We had previously found very good interobserver agreement in a review of 100 randomly selected echocardiograms by two echocardiographers.¹² The wall thickness was measured in the descending aorta, distal arch, proximal arch, and ascending aorta, and the thickest lesion was measured at each level. Since the ascending part of the aorta and the proximal arch are the regions that are most likely to be sources of cerebral emboli, we pooled the lesions located in these two regions of the thoracic aorta. We divided the patients into three groups according to the thickness of the wall of the ascending aorta or proximal arch: no plaques (wall thickness, <1 mm), plaques 1 to 3.9 mm thick, and plaques ≥ 4 mm thick.

Statistical Analysis

We used two-tailed t-tests and analysis of variance for comparisons of means, and chi-square tests for comparisons of proportions. The incidence of new events was expressed per 100 person-years of follow-up. We used the Kaplan-Meier method to estimate the distribution of time to events. Kaplan-Meier curves were compared with use of the log-rank test and the Mantel-Cox test for trend. We then constructed a Cox model including age (60 to 67, 68 to 73, 74 to 79, or ≥ 80 years), sex, cigarette-smoking status, peripheral arterial disease, atrial fibrillation, carotid stenosis (≤ 30 , 31 to 69, or ≥ 70 percent), aortic-arch plaques (<1, 1 to 3.9, or ≥ 4 mm in thickness), and treatment. We used this model to look for significant predictors of recurrent brain infarction and all vascular events and to calculate the relative risks adjusted for the presence of carotid stenosis, atrial fibrillation, peripheral arterial disease, and other confounding risk factors. The Cox model was constructed by entering independent variables

Table 1. Base-Line Characteristics of the Study Patients According to Plaque Thickness in the Aortic Arch Proximal to the Ostium of the Left Subclavian Artery.*

CHARACTERISTIC	PLAQUE THICKNESS (mm)			P VALUE†
	<1 (N = 143)	1-3.9 (N = 143)	≥ 4 (N = 45)	
Age — yr	74.3 $\pm$ 7.9	77.2 $\pm$ 7.4	78.0 $\pm$ 7.8	0.001
Female sex — no. (%)	71 (49.7)	79 (55.2)	25 (55.6)	0.592
Body-mass index‡	25.85 $\pm$ 3.98	24.47 $\pm$ 4.49	24.77 $\pm$ 4.16	0.059
High blood pressure — no. (%)	99 (69.2)	85 (59.4)	33 (73.3)	0.109
Diabetes mellitus — no. (%)	26 (18.2)	23 (16.1)	10 (22.2)	0.637
High serum cholesterol — no. (%)	38 (26.6)	49 (34.3)	15 (33.3)	0.343
Cigarette smoking — no. (%)	57 (39.9)	51 (35.7)	26 (57.8)	0.03
Previous brain infarction or transient ischemic attack — no. (%)	30 (21.0)	23 (16.1)	10 (22.2)	0.483
Previous myocardial infarction — no. (%)	12 (8.4)	14 (9.8)	4 (8.9)	0.918
Peripheral arterial disease — no. (%)	10 (7.0)	13 (9.1)	11 (24.4)	0.003
Atrial fibrillation — no. (%)	44 (30.8)	42 (29.4)	6 (13.3)	0.064
Carotid stenosis — no. (%)				
$\leq 30\%$	115 (81.0)§	95 (66.4)	28 (62.2)	0.015
31-69%	14 (9.9)§	22 (15.4)	11 (24.4)	
$\geq 70\%$	13 (9.1)§	26 (18.2)	6 (13.3)	0.081
Distal-arch plaque thickness — no. (%)				
<1 mm	64 (44.8)	5 (3.5)	1 (2.3)¶	<0.001
1-3.9 mm	73 (51.0)	123 (86.0)	8 (18.2)¶	
≥ 4 mm	6 (4.2)	15 (10.5)	35 (79.5)¶	
Descending-aorta plaque thickness — no. (%)				
<1 mm	12 (8.4)	1 (0.7)§	0¶	<0.001
1-3.9 mm	113 (79.0)	105 (73.9)§	18 (40.9)¶	
≥ 4 mm	18 (12.6)	36 (25.4)§	26 (59.1)¶	
Treatment since brain infarction at entry — no. (%)				
Antiplatelet	90 (62.9)	97 (67.8)	24 (53.3)	0.346
Anticoagulant	26 (18.2)	26 (18.2)	9 (20.0)	
Neither	27 (18.9)	20 (14.0)	12 (26.7)	

*Plus-minus values are means $\pm$ SD.

†P values refer to comparisons between the three groups.

‡Defined as the weight in kilograms divided by the square of the height in meters. Data were available for 104, 102, and 31 of the patients in the <1-mm, 1-to-3.9-mm, and ≥ 4 -mm groups, respectively.

§Data are based on the study of 142 patients.

¶Data are based on the study of 44 patients.

into the model whose coefficients were statistically significant at the 0.10 level and by removing variables whose coefficients were not significant at the 0.15 level. The data were analyzed with SAS and BMDP statistical software.^{13,16}

RESULTS

Among the 331 patients in the study, we found 143 with no plaques (wall thickness, <1 mm), 143 with plaques 1 to 3.9 mm in thickness, and 45 with plaques ≥ 4 mm in thickness in the aortic arch (proximal to the ostium of the left subclavian artery). As shown in Table 1, patients with plaques ≥ 4 mm in thickness were older and were more likely to be cigarette smokers and to have peripheral arterial disease or carotid stenosis of more than 30 percent than were patients with 1-to-3.9-mm plaques or no plaques, but they were less likely to have atrial fibrillation. No significant difference was found in the prevalence of carotid stenosis of ≥ 70 percent.

The mean follow-up was 2.4 years, with a total follow-up of 788 person-years. Eighty-two percent of the patients received antithrombotic therapy (64 percent received an antiplatelet drug and 18 percent an antico-

agulant); most of the remaining 18 percent had contraindications to antithrombotic therapy. Patients with a mobile lesion in the aortic arch received warfarin for one to three months and aspirin thereafter. Five patients underwent carotid endarterectomy. There were no significant differences among the three groups in the proportions of patients given antiplatelet, anticoagulant, or no therapy (Table 1). The numbers of new events and the rates of events per 100 person-years are shown according to plaque thickness in Tables 2 and 3.

Recurrent Brain Infarction

The incidence of recurrent brain infarction was 11.9 per 100 person-years of follow-up in patients with plaques ≥ 4 mm thick, as compared with 3.5 per 100 person-years in patients with plaques 1 to 3.9 mm thick, and 2.8 per 100 person-years in patients with no plaques (wall thickness, < 1 mm) (Table 3). The three Kaplan-Meier curves (Fig. 1) were significantly different from one another ($P < 0.001$) and remained so after stratification based on age ($P = 0.0029$). In the Cox model, the presence of aortic-arch plaques ≥ 4 mm thick was an independent predictor of recurrent brain infarction (relative risk, 3.8; 95 percent confidence interval, 1.8 to 7.8; $P = 0.0012$) after adjustment for the presence of carotid stenosis, atrial fibrillation, peripheral arterial disease, type of treatment, and other confounding factors.

All Vascular Events

The incidence rates of all vascular events were 26.0, 9.1, and 5.9 per 100 person-years of follow-up in patients with plaque thicknesses of ≥ 4 mm, 1 to 3.9 mm, and < 1 mm, respectively (Table 3). The three Kaplan-Meier curves (Fig. 2) were significantly different from one another ($P < 0.001$) and remained so after stratifica-

Table 2. Number of Events in the Study Patients According to Plaque Thickness in the Aortic Arch Proximal to the Ostium of the Left Subclavian Artery.

EVENT	PLAQUE THICKNESS (mm)		
	< 1 (N = 143)	1-3.9 (N = 143)	≥ 4 (N = 45)
	no. of events		
Recurrent brain infarction	10	11	11
Myocardial infarction	3	3	6
Peripheral embolism	4	4	4
All deaths	35	52	23
After qualifying stroke	8	14	3
Vascular cause (including sudden death)	12	16	14
Unknown cause	3	1	0
Nonvascular cause	12	21	6
Myocardial infarction and sudden death	5	13	8
Any vascular event*	21	28	23

*Includes brain infarction, myocardial infarction, peripheral embolism, and death from vascular causes.

Table 3. Incidence of Events According to Plaque Thickness in the Aortic Arch Proximal to the Ostium of the Left Subclavian Artery.

PLAQUE THICKNESS (mm)	RECURRENT BRAIN INFARCTION			ANY VASCULAR EVENT*		
	PERSON-YEARS OF FOLLOW-UP†	NO. OF EVENTS	INCIDENCE PER 100 PERSON-YEARS OF FOLLOW-UP	PERSON-YEARS OF FOLLOW-UP†	NO. OF EVENTS	INCIDENCE PER 100 PERSON-YEARS OF FOLLOW-UP
< 1	359.3	10	2.8	354.0	21	5.9
1-3.9	312.6	11	3.5	308.2	28	9.1
≥ 4	92.4	11	11.9	88.4	23	26.0

*Includes brain infarction, myocardial infarction, peripheral embolism, and death from vascular causes.

†Differences between the total person-years of follow-up in each category of plaque thickness are due to censored data at the time of the first event.

tion based on age ($P < 0.001$). The multivariate analysis showed that the presence in the aortic arch of plaques ≥ 4 mm thick was an independent predictor of new vascular events (relative risk, 3.5; 95 percent confidence interval, 2.1 to 5.9; $P < 0.001$). In the multivariate analysis, atrial fibrillation (relative risk, 3.3; 95 percent confidence interval, 1.4 to 3.8; $P = 0.0013$) and carotid stenosis of 70 percent or more (relative risk, 2.9; 95 percent confidence interval, 1.8 to 3.4; $P = 0.0023$) were also independent predictors of new vascular events.

Patients with Brain Infarction of Unknown Cause at Entry

Of the 102 patients who had brain infarction of unknown cause at entry, those who had plaques ≥ 4 mm thick in the aortic arch had a higher incidence of recurrent brain infarction (16.4 per 100 person-years of follow-up) and of all vascular events (26.1 per 100 person-years of follow-up) than those who had plaques of 1 to 3.9 mm or no plaques ($P = 0.0066$) (Table 4 and Fig. 3). After adjustment for age, sex, cigarette-smoking status, type of treatment, peripheral arterial disease, atrial fibrillation, and carotid stenosis, the multivariate analysis showed that the presence in the aortic arch of plaques ≥ 4 mm thick was an independent predictor of both recurrent brain infarction (relative risk, 5.2; 95 percent confidence interval, 1.7 to 15.6; $P = 0.0042$) and all vascular events (relative risk, 6.0; 95 percent confidence interval, 2.4 to 14.9; $P < 0.001$).

DISCUSSION

We found that patients with brain infarction and plaques ≥ 4 mm thick in the aortic arch had a recurrence rate of 11.9 per 100 person-years of follow-up and an incidence of all vascular events of 26.0 per 100 person-years of follow-up. These incidence rates are among the highest reported in patients with ischemic stroke treated with antiplatelet drugs, including those with nonvalvular atrial fibrillation in the European Atrial Fibrillation Trial (10 percent per year for brain infarction)¹⁷ and those with uncorrected carotid stenosis of at least 70 percent in the North American Symptomatic Carotid Endarterectomy Trial (13 percent per year

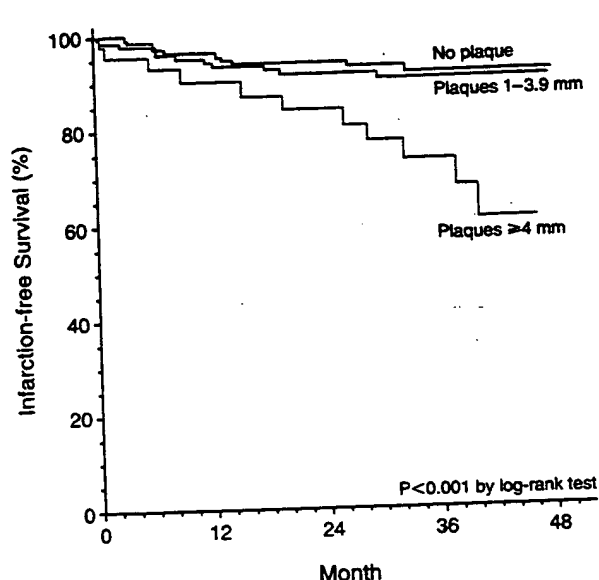


Figure 1. Kaplan-Meier Analysis of Survival without Recurrent Brain Infarction, According to Plaque Thickness in the Aortic Arch Proximal to the Ostium of the Left Subclavian Artery.

for ipsilateral brain infarction).¹⁸ Most of our patients also received antiplatelet therapy. This may have led to an underestimation of the natural rate of recurrence, but we thought it would be unethical not to treat these patients, since a 25 percent decrease in the rate of recurrence has been reported in patients with ischemic stroke related to atherosclerosis who are given antiplatelet drugs.¹⁹ Among our patients with plaques ≥ 4 mm thick in the aortic arch, we found no significant differences in event rates between those receiving warfarin and those receiving aspirin, but few patients received warfarin, and our study was not designed as a therapeutic trial.

The proportion of smokers at base line among the patients with plaques of ≥ 4 mm was remarkably high (Table 1), which contrasts with the weak association found between cigarette smoking and carotid atheroma in most epidemiologic studies. This result is consistent with the fact that peripheral arterial disease was more common in these patients than in the other two study groups. By contrast, we found no difference among our three groups of patients with regard to hypertension or plasma cholesterol levels. One of the striking differences between our study and that of Tunick et al.¹⁴ is that none of our patients had symptomatic bowel or retinal embolism, although we looked for both. This discrepancy is probably ascribable to differences in recruitment in the two series. The qualifying vascular event in all our patients was brain infarction, whereas it was embolism to any organ in the patients studied by Tunick et al.¹⁴ Only one of our patients with plaques ≥ 4 mm thick in the aortic arch had clinically evident cholesterol embolism with renal infarcts. This patient was not receiving

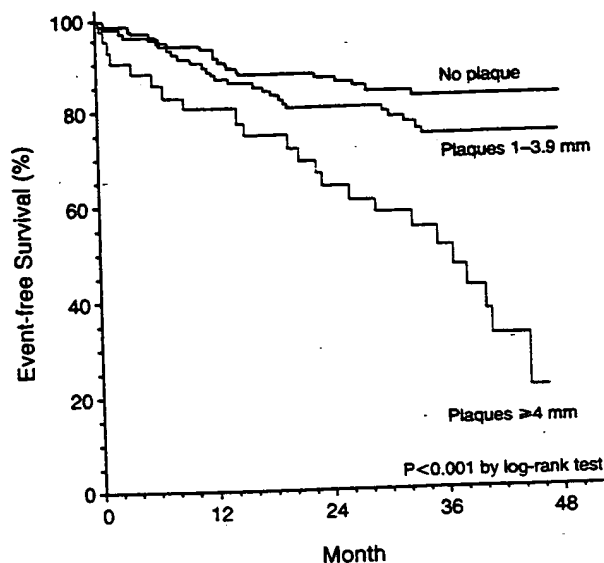


Figure 2. Kaplan-Meier Analysis of Survival without Vascular Events (Brain Infarction, Myocardial Infarction, Peripheral Embolism, or Death from Vascular Causes), According to Plaque Thickness in the Aortic Arch Proximal to the Ostium of the Left Subclavian Artery.

warfarin. There have been anecdotal reports of cholesterol embolism with blue-toe syndrome in patients with aortic atheroma treated with anticoagulants.^{20,21}

In our study, multivariate analysis showed that the presence of plaques ≥ 4 mm thick in the aortic arch was a predictor of recurrent brain infarction, independently of the presence of carotid stenosis, atrial fibrillation, and peripheral arterial disease. The significant differences among the Kaplan-Meier curves in the three study groups are additional evidence supporting a causal link between plaques of this size and brain infarction in some patients. Such a link has been suggested by reports of systemic embolism in patients who had a stroke after a surgical procedure with cardiopulmonary bypass^{5,22-24} or after angiography.^{25,26} In addition, sys-

Table 4. Incidence of Events in 102 Patients with Brain Infarctions of Unknown Cause, According to Plaque Thickness in the Aortic Arch Proximal to the Ostium of the Left Subclavian Artery.

PLAQUE THICKNESS (mm)	RECURRENT BRAIN INFARCTION			ANY VASCULAR EVENT*		
	PERSON-YEARS OF FOLLOW-UP†	NO. OF EVENTS	INCIDENCE PER 100 PERSON-YEARS OF FOLLOW-UP	PERSON-YEARS OF FOLLOW-UP†	NO. OF EVENTS	INCIDENCE PER 100 PERSON-YEARS OF FOLLOW-UP
<1	116.0	5	4.3	115.9	6	5.2
1-3.9	69.2	1	1.5	69.1	3	4.3
≥ 4	42.6	7	16.4	42.2	11	26.1

*Includes brain infarction, myocardial infarction, peripheral embolism, and death from vascular causes.

†Differences between the total person-years of follow-up in each category of plaque thickness are due to censored data at the time of the first event.

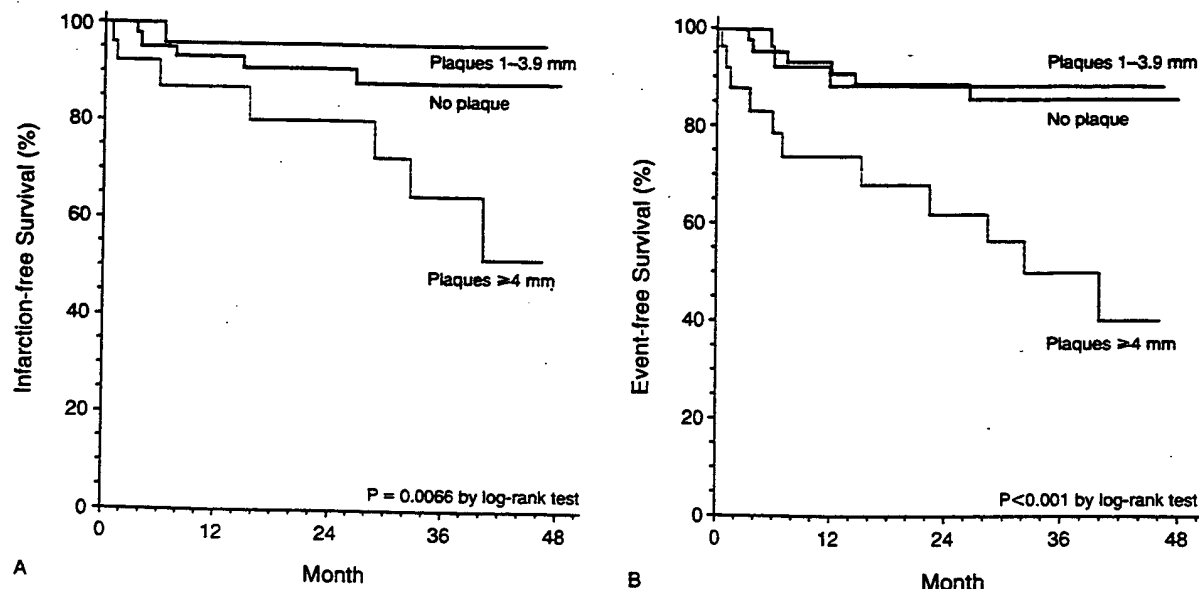


Figure 3. Kaplan-Meier Analysis of Survival without Recurrent Brain Infarction (Panel A) and Vascular Events (Panel B) in 102 Patients with Qualifying Brain Infarctions of Unknown Cause, According to Plaque Thickness in the Aortic Arch Proximal to the Ostium of the Left Subclavian Artery.

temic embolism has been reported in patients with no detectable source of emboli other than aortic-arch atheroma.^{1,27-35} However, our study also showed that the presence in the aortic arch of plaques ≥ 4 mm thick was a strong independent predictor of vascular events of all types, leading us to the conclusion that it is above all a good marker of severe generalized atherosclerotic disease that could be used to select patients at high risk for vascular events.

Brain infarction of unknown cause accounts for one third of ischemic strokes in patients 60 years of age or older.¹² The high risk of vascular events (recurrence of stroke and other events) in our patients of that age who had plaques of ≥ 4 mm in the aortic arch may have important implications for preventive therapy. The relative benefits and risks of therapeutic interventions in these patients should now be evaluated.

APPENDIX

The following institutions and investigators participated in the French Study of Aortic Plaques in Stroke: Paris — Hôpital Saint-Antoine, Pierre and Marie Curie University: *Department of Neurology* — P. Amarenco (principal investigator), O. Heinzel, C. Lucas, and P.-J. Touboul (cranial ultrasound study design), J.-L. Gérard, V. Adrai, D. Rougemont, and M.-G. Bousser; *Department of Cardiology* — A. Cohen (co-principal investigator), C. Chauvel, B. Benhalima, C. Albo, and E. Abergel. Grenoble — Centre Hospitalier et Universitaire de Grenoble: *Stroke Unit* — M. Hommel (local principal investigator), G. Besson, and L. Vercueil; *Department of Cardiology* — B. Bertrand (local co-principal investigator). Besançon — Centre Hospitalier et Universitaire de Besançon: *Department of Neurology, Jean Minjot Hospital* — T. Moulin (local principal investigator), D. Chavot, and L. Tatu; *Department of Cardiology, Saint-Jacques Hospital* — Y. Bernard (local co-principal investigator). Lille — Centre Hospitalier et Universitaire de Lille: *Department of Neurology, Robert Salengro Hospital* — D. Leys (local

principal investigator), P. Rondepierre, and C. Lucas; *Department of Cardiology, Cardiology Hospital* — L. Goulard (local co-principal investigator), G. Deklunder, and E. Chamas. Dijon — Centre Hospitalier et Universitaire de Dijon: *Department of Cardiology, Bocage's Hospital* — S. Falcon (local principal investigator) and J.-E. Wolf; *Department of Neurology, General Hospital* — M. Giroud. *Echocardiography Reviews* — Ariel Cohen (echocardiographic study design and review of all echocardiographic examinations), B. Bertrand, C. Chauvel, and Y. Bernard. *Data Monitoring and Coordinating Center* — P. Amarenco. *Data Analysis* — C. Tzourio, INSERM Unité 360, Recherches Epidémiologiques en Neurologie et Psychopathologie, Paris. *Authors* — P. Amarenco (principal investigator and study design), A. Cohen (co-principal investigator), M. Hommel (study design), T. Moulin, D. Leys, and M.-G. Bousser.

REFERENCES

1. Tunick PA, Kronzon I. Protruding atherosclerotic plaque in the aortic arch of patients with systemic embolization: a new finding seen by transesophageal echocardiography. *Am Heart J* 1990;120:658-60.
2. Karalis DG, Chandrasekaran K, Victor MF, Ross JJ Jr, Mintz GS. Recognition and embolic potential of intraaortic atherosclerotic debris. *J Am Coll Cardiol* 1991;17:73-8.
3. Tunick PA, Perez JL, Kronzon I. Protruding atheromas in the thoracic aorta and systemic embolization. *Ann Intern Med* 1991;115:423-7.
4. Tunick PA, Lackner H, Katz ES, Culliford AT, Giangola G, Kronzon I. Multiple emboli from a large aortic arch thrombus in a patient with thrombotic diathesis. *Am Heart J* 1992;124:239-41.
5. Katz ES, Tunick PA, Rusinek H, Ribakove G, Spencer FC, Kronzon I. Protruding aortic atheromas predict stroke in elderly patients undergoing cardiopulmonary bypass: experience with intraoperative transesophageal echocardiography. *J Am Coll Cardiol* 1992;20:70-7.
6. Amarenco P, Cohen A, Baudrimont M, Bousser M-G. Transesophageal echocardiographic detection of aortic arch disease in patients with cerebral infarction. *Stroke* 1992;23:1005-9.
7. Horowitz DR, Tuhim S, Budd J, Goldman ME. Aortic plaque in patients with brain ischemia: diagnosis by transesophageal echocardiography. *Neurology* 1992;42:1602-4.
8. Toyoda K, Yasaka M, Nagata S, Yamaguchi T. Aortogenic embolic stroke: a transesophageal echocardiographic approach. *Stroke* 1992;23:1056-61.
9. Nihoyannopoulos P, Joshi J, Athanasopoulos G, Oakley CM. Detection of atherosclerotic lesions in the aorta by transesophageal echocardiography. *Am J Cardiol* 1993;71:1208-12.

10. Dávila-Román VG, Barzilai B, Wareing TH, Murphy SF, Schechtman KB, Kouchoukos NT. Atherosclerosis of the ascending aorta: prevalence and role as an independent predictor of cerebrovascular events in cardiac patients. *Stroke* 1994;25:2010-6.
11. Amarenco P, Druyckaerts C, Tzourio C, Hénin D, Bousser M-G, Hauw J-J. The prevalence of ulcerated plaques in the aortic arch in patients with stroke. *N Engl J Med* 1992;326:221-5.
12. Amarenco P, Cohen A, Tzourio C, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med* 1994;331:1474-9.
13. Jones EF, Kalman JM, Calafiore P, Tonkin AM, Donnan GA. Proximal aortic atheroma: an independent risk factor for cerebral ischemia. *Stroke* 1995;26:218-24.
14. Tunick PA, Rosenzweig BP, Katz ES, Freedberg RS, Perez JL, Kronzon I. High risk for vascular events in patients with protruding aortic atheromas: a prospective study. *J Am Coll Cardiol* 1994;23:1085-90.
15. SAS user's guide: version 6. 4th ed. Vol. 1. Cary, N.C.: SAS Institute, 1989.
16. Dixon WJ, ed. BMDP statistical software manual. Berkeley: University of California Press, 1992.
17. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993;342:1255-62.
18. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445-53.
19. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106. [Erratum, *BMJ* 1994;308:1540.]
20. Feder W, Auerbach R. "Purple toes": an uncommon sequela of oral coumarin drug therapy. *Ann Intern Med* 1961;55:911-7.
21. Bruns FJ, Segel DP, Adler S. Control of cholesterol embolization by discontinuation of anticoagulant therapy. *Am J Med Sci* 1978;275:105-8.
22. Price DL, Harris J. Cholesterol emboli in cerebral arteries as a complication of retrograde aortic perfusion during cardiac surgery. *Neurology* 1970;20:1209-14.
23. McKibbin DW, Gott VL, Hutchins GM. Fatal cerebral atheromatous embolization after cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1976;71:741-5.
24. Gardner TJ, Horneffer PJ, Manolio TA, et al. Stroke following coronary artery bypass grafting: a ten-year study. *Ann Thorac Surg* 1985;40:574-81.
25. Cogan DG, Kuwabara T, Moser H. Fat emboli in the retina following angiography. *Arch Ophthalmol* 1964;71:308-13.
26. Ramirez G, O'Neill WM Jr, Lambert R, Bloomer HA. Cholesterol embolization: a complication of angiography. *Arch Intern Med* 1978;138:1430-2.
27. Winter WJ. Atheromatous emboli: a cause of cerebral infarction: report of two cases. *Arch Pathol* 1957;64:137-42.
28. Gore I, Collins DP. Spontaneous atheromatous embolization: review of the literature and a report of 16 additional cases. *Am J Clin Pathol* 1960;33:416-26.
29. Sturgill BC, Netsky MG. Cerebral infarction by atheromatous emboli: case report and review of literature. *Arch Pathol* 1963;76:189-96.
30. Soloway HB, Aronson SM. Atheromatous emboli to central nervous system. *Arch Neurol* 1964;11:657-67.
31. David NJ, Klinworth GK, Friedberg SJ, Dillon M. Fatal atheromatous cerebral embolism associated with bright plaques in the retinal arterioles. *Neurology* 1963;13:708-13.
32. Hollenhorst RW. Vascular status of patients who have cholesterol emboli in the retina. *Am J Ophthalmol* 1966;61:1159-65.
33. Case Records of the Massachusetts General Hospital (Case 25-1967). *N Engl J Med* 1967;276:1368-77.
34. Case Records of the Massachusetts General Hospital (Case 21-1972). *N Engl J Med* 1972;286:1146-53.
35. Beal MF, Williams RS, Richardson EP Jr, Fisher CM. Cholesterol embolism as a cause of transient ischemic attacks and cerebral infarction. *Neurology* 1981;31:860-5.

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